

VALUE OF TREATMENT IN REITER'S DISEASE *

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It is now established that similar clinical syndromes consisting of non-specific urethritis, conjunctivitis, and arthritis may occur either in association with bacillary dysentery or in the absence of any signs or recent history of bowel disorder, and it has become customary to refer to both syndromes as Reiter's disease or Reiter's syndrome. The aetiology of Reiter's disease is obscure and opinion is divided as to whether it has one or many causes, and whether there is any effective treatment for the condition. This paper deals with the therapeutic problem.

For many years artificial fever has been regarded as an effective form of therapy, particularly in Great Britain. Successful results have also been claimed for penicillin (Freireich, Schwartz, and Steinbrocker, 1947), streptomycin (Thompson, White, and Hailey, 1949), antihistamines alone and combined with streptomycin (Levy, 1951), the wide-spectrum antibiotics (Korb and Brown, 1950; Findlay and Willcox, 1951; Harkness, 1953), gold salts (Willcox, Findlay, and Henderson-Begg, 1947), and cortisone and ACTH (Ogryzlo and Graham, 1950; Myerson and Katzenstein, 1952).

Most of these claims, however, have been based upon the results of treatment in a few cases, and at times in a single case, and when assessing these results little attention has been paid to the fact that Reiter's disease tends to regress spontaneously after weeks or months and seldom persists for longer than 6 to 7 months (Vallee, 1946; Ford, 1953). In a comprehensive review of the literature Vallee concluded that neither penicillin, fever therapy, nor any other therapeutic measure in use at that time had any effect upon the course of the illness. Ford agreed that penicillin was valueless and believed that the wide-spectrum antibiotics were equally ineffective. Ford also doubted the value of fever therapy, but considered that cortisone and ACTH might produce temporary suppression of clinical signs.

Clinical Material

This consisted of 73 male and two female patients aged from 20 to 55 years. No patient had a recent history of dysentery or of gonorrhoea. Non-specific urethritis and acute hydrarthrosis of at least one joint were present in every case. Ocular and cutaneous manifestations were each present in 22 cases, but only in five cases were both present. Five patients had no treatment other than rest in bed, and the remaining seventy had one or more types of systemic therapy.

Duration of Illness

The approximate duration of the illness is shown in Table I. One of the five patients from whom treatment was withheld recovered in 2 weeks, two cases in 3 weeks, and the others in 4 and 6 weeks.

TABLE I
DURATION OF ILLNESS IN 75 CASES

Duration of Illness	Weeks			Months											
	1	2	3	1	2	3	4	5	6	7	11	18	36	48	
No. of Cases	0	6	10	13	15	10	6	5	4	2	1	1	1	1	

Therapy

Table II (opposite) shows the initial treatment, the total number of cases given each type of treatment, and the number of patients who recovered during or within 7 days of the completion of each particular treatment.

Sulphathiazole and the Antibiotics.—In ten cases sulphathiazole, given when urethritis was the only feature present, failed to prevent the syndrome progressing.

Seven of the patients treated with penicillin had this treatment when urethritis alone was present. Three patients recovered after streptomycin therapy (6, 8, and 15 g. respectively). Joint signs disappeared but genito-urinary signs persisted in one patient who was given 26 g. streptomycin. There was a temporary improvement of the arthritis in three cases, two of whom were given 15 g. and the other 25 g. streptomycin; the other features, however, were unaffected.

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TABLE II
RESULTS OF VARIOUS TYPES OF TREATMENT

Therapy	Dosage	Initial Treatment		Total Treatment	
		No. of Cases	Recovered	No. of Cases	Recovered
Sulphathiazole	20 g. (1 g.-6 hourly)	17	2	27	4
Penicillin	2-5 m.u. (0.5 m.u. daily or twice daily)	13	—	13	—
Streptomycin	3-25 g. (0.5 g. twice daily)	6	1	20	3
Chloramphenicol	8-10 g. (0.5 g.-6 hourly)	4	1	5	1
Aureomycin	8-24 g.	5	—	8	1
Terramycin	8-14 g.	12	2	20	4
Fever	6-10 bouts	10	2	45	20*
NAB	0.9 g. (0.3 g. alternate days)	1	—	8	1
Benadryl	2.1 g. (0.1 g. three times a day)	2	1	2	1
Anthisan	2.8 g. (0.1 g. four times a day)	—	—	2	—
Phenergan	1.4 g. (0.1 g. twice a day)	—	—	3	—
P. aminobenzoic acid ..	36 g. (2 g. three times a day)	—	—	2	—
Butazolidin	2.8 g. (0.1 g.-6 hourly)	—	—	3	—
ACTH	1.2-1.8 g. (0.1 g. daily)	—	—	4	1
Gold Salts	1.5 g. (0.1 g. weekly)	—	—	4	1
Salicylates	20 gr. three or four times a day	—	—	15	—

* Fourteen cases recovered after one course of treatment. Six cases recovered after two courses of treatment.

In another patient an extension of the arthritis occurred after he had had 25 g. streptomycin, one case was cured after chloramphenicol (8 g.), but in the others the course of the illness was not influenced by chloramphenicol.

One patient recovered after having had aureomycin (8 g.). Keratoderma blennorrhagica developed in another patient after 24 g. aureomycin.

Four cases recovered after being given 8 g. terramycin. The same amount of terramycin, however, did not prevent the syndrome progressing when given for urethritis in four cases with a past history of Reiter's disease. In another patient with a past history of the syndrome, the present attack commenced with iritis and urethritis, and arthritis appeared after he had had 13 g. terramycin. In one case the joints recovered during this treatment, but the other features which also included iritis showed no improvement. Six patients had two courses of terramycin: in one of these the joints improved markedly during the first course, but fresh joints were affected during the second course. In another case the joints recovered during the second course, but the genito-urinary signs persisted and the arthritis recurred 7 days after this treatment had been completed.

Fever Therapy.—Six to ten intravenous injections of TAB (typhoid vaccine) or gonococcal vaccine (15 to 175 million organisms) were given over a period

of 10 to 20 days. In nine cases this treatment produced no beneficial effects and in one case the joint pains were increased, while in another an extension of the arthritis occurred during this course of treatment. In the other 36 cases there was an immediate and often marked improvement, especially of the arthritis, after each bout of fever. Only fourteen patients, however, returned to normal following one course of fever therapy. Six patients were greatly improved at the end of the first course and recovered during a second course. In three cases, in which fresh joints were involved during or immediately after the first course, a second course proved valueless. In another patient given two courses of fever the arthritis extended during the second course. Three courses of fever therapy failed to shorten the illness in a case in which this lasted for 11 months.

NAB (Novarsenobillon) was the first treatment prescribed for a patient who had symptoms and signs suggestive of abacterial pyuria, but had no effect upon the urinary condition. One patient treated with Benadryl made a prompt recovery; the other developed keratoderma blennorrhagica during treatment. The other antihistamines and para-aminobenzoic acid exerted no influence upon the course of the illness. Butazolidin was completely unsuccessful in one case but produced marked alleviation of joint symptoms in the other

two cases ; this beneficial effect disappeared when the drug was withheld.

ACTH produced no response in two cases. In one case joint signs disappeared and the evolution of keratoderma blennorrhagica ceased at the pustular stage. The eruption persisted, however, and went on to crust formation when ACTH was discontinued. The signs of acute hydrarthrosis also returned at this time. The second patient had been ill for 10 months and the disease was in a subacute phase when ACTH was administered. Symptoms disappeared after 3 days of treatment and did not recur when this was stopped, although a small effusion persisted in both knee joints and the prostatic secretion contained many pus cells.

The illness had been present for at least 2 months before gold therapy was tried. One patient recovered after three injections of Myocrysin but relapsed 2 months later. The other three patients made a steady but gradual recovery over 6 to 8 weeks. One has remained well since, and the other two have recently suffered from a fresh attack of the syndrome.

Salicylates (sodium salicylate or calcium aspirin) were prescribed for usually 2 or 3 weeks when alternative therapy had proved ineffective. Apart from the analgesic effect, especially of calcium aspirin in the larger doses, this treatment had no noticeable influence upon the illness, although three patients began to recover towards the end of the treatment period and were completely cured soon after its conclusion.

The literature contains many reports of cases in which other constituents of the syndrome appeared after sulphonamide or penicillin therapy for urethritis, and as many reports of cases in which sulphonamides and penicillin had no effect upon the established syndrome, and it is now generally accepted that neither of these is an effective treatment for Reiter's disease. It is also the general opinion that arsenical therapy is of little value, although it has been claimed that this treatment has a beneficial effect on the bladder condition at times (Baines, 1947). The results obtained with streptomycin and the wide-spectrum antibiotics by authors already mentioned and by Warthin (1948), Dienes, Ropes, Smith, Madoff, and Bauer (1948), Coodley, Weiss, and Egeberg (1948), Willcox and Findlay (1952a, b), and Wheatley (1953) are shown in Table III. It should be noted, however, that in some instances our interpretation of the effects of therapy differs from those of the authors, *e.g.*, the case of Thompson and his colleagues (1949) and a case of Findlay and Willcox (1951) and Willcox and Findlay (1952b) have been regarded as not res-

TABLE III
RESULTS OF TREATMENT WITH ANTIBIOTICS

Antibiotic	Total No. of Cases	No. of Cases Cured
Streptomycin	25	5
Aureomycin	24	6
Chloramphenicol	6	1
Terramycin	15	7

ponding to streptomycin, chloramphenicol, and terramycin respectively because of the length of time signs persisted after treatment.

The results of streptomycin, aureomycin, and chloramphenicol therapy in these cases are very similar to those obtained by us and need not be discussed further, except to note that both streptomycin (Levy, 1951) and aureomycin (Ford, 1953) failed to arrest the syndrome when urethritis was the sole manifestation. Terramycin (12 g.) had no effect in the case reported by Myerson and Katzenstein (1952). Willcox and Findlay (1952a, b) described the effects of terramycin in five cases ; in one case recovery followed 12.5 g. terramycin, while 6, 12.5, and 19.5 g. respectively had little or no effect in three cases, and arthritis developed in the remaining case after 6 g. terramycin had been given for urethritis. Harkness (1953) treated nine patients with 20 and 28 g. terramycin ; four of these had not had any previous treatment and all recovered. The other five had been treated by other methods before terramycin was prescribed and two recovered with this antibiotic.

Fever therapy proved unsuccessful in eleven out of thirteen cases described by the authors already mentioned. Successful claims are more difficult to assess, as few cases seem to have been given this treatment until other measures had failed, and generally no mention is made of the time which elapsed between treatment and complete recovery. Thus Harkness (1945) attributes recovery in many cases to induced fever although the average duration of the illness in these cases would appear to be about 2 months, while King, Williams, Nicol, and Loudon (1946) give no indication of the duration of the illness. King and his colleagues found that fever induced with TAB vaccine cured 25 out of 32 cases, but that only 41 patients recovered out of a total of 79 treated by mechanically induced hyperthermia. These authors note that a number of cases treated by the latter method had failed to respond previously to TAB vaccine.

As far as we can ascertain, the only paper which deals with antihistamine therapy in Reiter's disease is that of Levy (1951) : four cases had 1.05 to 1.8 g.

Phenergan combined with 7.5 to 10.5 g. streptomycin. The duration of the illness in these cases was 17, 32, 42, and not less than 35 days. In all four cases the joints improved considerably during treatment. Pyuria persisted in three cases, however, and required local treatment. In one of these cases the erythrocyte sedimentation rate was 65 mm./hr before treatment commenced and 97 mm./hr 16 days later, while in another the erythrocyte sedimentation rate was 28 mm./hr 19 days after treatment was begun.

The other two patients had failed to respond to streptomycin earlier in the illness and were given Phenergan by itself. In one case the duration of the illness was about 5 months and Phenergan therapy was commenced after the illness had persisted for 4 months. The duration of the illness in the other case was 38 days; in this case the joint condition improved during this treatment but pyuria persisted and further treatment was given.

Ford (1953) treated six cases with ACTH or cortisone and found that both hormones suppressed the various manifestations of the syndrome. In one case, however, ACTH (750 mg. in 5 days) and cortisone (1,000 mg. in 5 days) had no beneficial effect when given early in the illness, but did have a suppressive effect after the illness had been present for 80 days. The illness had been present for 3 months in the case reported by Myerson and Katzenstein (1952) when hormone therapy was instituted. A course of 1,800 mg. cortisone in 11 days was followed at monthly intervals by two courses of ACTH (1,360 mg. in 17 days). The lesions of keratoderma blennorrhagica were unchanged with cortisone. The arthritis improved, however, but relapsed as soon as the hormone was withdrawn. General improvement occurred during each course of ACTH; there was a prompt relapse when it was discontinued the first time, but improvement was maintained and recovery followed the second course. Two patients, in whom the illness had been present for 11 weeks and almost 4 months respectively, were given 100 mg. ACTH daily for 12 days and 40 mg. daily for 14 days respectively (Ogryzlo and Graham, 1950). In both cases signs were suppressed by the hormone and recurred but with less severity when this was withdrawn. Both made a complete recovery during the following month. Hormone therapy was instituted in the third case treated by these authors after the illness had been present for 18 days. Daily doses of 100 mg. ACTH for 14 days were followed after 8 days by 4.4 g. cortisone in 23 days, and 2 months later a second course of cortisone was given. Improvement occurred during each course of treatment, but severe relapse followed withdrawal of the

hormones on the first two occasions. Less severe signs reappeared when cortisone was discontinued for the second time.

Willcox and his colleagues (1947) treated two cases with Myocrysin and both gradually recovered. Harkness (1950) treated eight cases with gold salts; one case made a prompt recovery, but in the others the course of the illness was unaltered.

A large number of patients have been given salicylates, usually without success, although Harkness (1950) has noted rapid recoveries at times during this treatment.

Discussion

Ford (1953) states that Reiter's disease remits spontaneously but may persist for 1 to 7 months before doing so. The duration of the illness in three of our five untreated cases shows the correctness of the implication that spontaneous remission may occur in less than a month. Only in these three cases and in thirteen treated cases was the illness present for less than a month, so that treatment did not produce any marked reduction in the duration of the illness in the majority of these cases. Further, the number of recoveries which followed sulphathiazole, antibiotic, and arsenical therapy was so small as to suggest that these were, in fact, spontaneous. The alternative to this is that the illness in these cases was due to an infection sensitive to one or other of these therapeutic agents, but there was no bacteriological evidence of this. As was mentioned earlier, it is generally accepted that neither sulphonamide, penicillin, nor arsenical therapy is of value. It is seen from Tables I, II, and III that the number of our cases in which recovery followed streptomycin, aureomycin, and chloramphenicol therapy is very similar to that generally obtained and that the experience of Willcox and Findlay (1952a, b) with terramycin is also in agreement with ours. The higher recovery rate achieved with terramycin by Harkness (1953) is unlikely to be due to a higher total dosage, as almost the same amount had no effect in a case of Willcox and Findlay (1952a) and in some of our cases fresh manifestations appeared during treatment, although the daily amount of terramycin was similar to that prescribed by Harkness (1953). Only nine cases were treated by Harkness (1953), and we would suggest that with this small number of cases the high recovery rate might have owed nothing to terramycin but was due to chance.

We would instance as another example of chance behaviour the failure of any of our cases to recover during penicillin treatment as spontaneous cure might have been expected, and indeed cases have

recovered rapidly during treatment with this antibiotic, e.g., a previous attack of the syndrome in the case reported by Korb and Brown (1950).

The number of recoveries following one course of induced fever was higher than that following any other form of treatment. However, in a self-limiting disease the results of initial treatment must give a better indication of the value of the treatment than results obtained later in the illness, and in our hands fever therapy was no more effective than the antibiotics when given at the start of the illness. This treatment was also incapable of limiting the disease in a number of our cases and, when it is considered that it was usually given after the illness had been present for some time and over a period of from 12 to 20 days, it is seen that the slightly higher recovery rate following fever therapy is of no significance and that there is no proof that this is an effective treatment for Reiter's disease. This finding is in accord with our impression of the reported results of fever therapy and we give as supportive evidence the fact that in the cases treated by King and his colleagues (1946) fever induced by TAB vaccine was followed by a higher proportion of recovery than fever induced by mechanical means, although the latter method maintains the temperature at a higher level for a longer period.

There is little need to discuss in detail the value of the other therapeutic measures used. It is obvious that there is no proof that antihistamines alone or combined with streptomycin, ACTH, or cortisone shorten the duration of the illness, although at times these hormones can produce temporary suppression of symptoms and signs. The evaluation of any prolonged treatment in a disease such as this is difficult, but the results of Myocrysin therapy obtained by Harkness (1950) and by us do not suggest that gold salts have any beneficial effect. Finally, as we have noted earlier, there are no indications that the salicylates have more than an analgesic action, and we would suggest that the prompt recoveries which Harkness (1950) saw occur at times during this treatment, and which he thought probably indicated misdiagnoses, were excellent examples of the self-limiting tendency of Reiter's disease.

In our introductory remarks we pointed out that many of the claims for therapeutic efficacy had been based upon the findings in a very few cases and

even in single cases and with little or no regard to the natural history of the illness. It is clear that in a self-limiting disease the fact that some particular form of treatment was not of value may be significant. However, before any treatment could be considered effective, it would be necessary to show that the illness was materially shortened in a large series of cases. We are conscious that some therapeutic agents have been excluded by us on the results of only a few cases, but none of these treatments proved satisfactory and even those types of treatments which were used in large numbers of cases also proved in our hands to have no material effect upon the illness.

Conclusion

The effect of various types of treatments has been assessed in seventy cases of Reiter's disease. The duration of the illness was no shorter than in five untreated cases, and we have found no evidence that any form of therapy at present in use has any influence upon the course of the illness.

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